REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Applicants gratefully acknowledge the July 20, 2006, personal interview with Examiner Turner, Michael L. Goldman, Esq., Shelley A. Jones, Esq., and Robert Bryant, Ph.D. The substance of the interview is summarized below.

Claims 17, 25–33, and 36 have now been canceled. Claims 37–41 are pending.

The rejection of claims 17, 25–33, and 36–41 under 35 U.S.C. § 101 for lack of utility is respectfully traversed in view of the above amendments.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the present application does not set forth a specific and substantial utility, because the present application does not contain any experimentation to confirm the function of TRP8 or that a membrane potential assay has any interpretable use with regard to bitter taste. Applicants respectfully disagree.

The present application teaches at, *e.g.*, paragraphs [0008], [0038], and [0055], that TRP8 participates in the taste signal transduction pathway and can be used to identify compounds that induce the perception of a bitter taste. This is confirmed by experimental work set forth in the accompanying Declaration of Robert W. Bryant, Ph. D. under 37 C.F.R. § 1.132 ("Bryant Declaration"). In particular, two groups of mice were tested for their aversion to denatonium and quinine, two bitter compounds, using a short access lickometer test, which measures the frequency with which the mice lick solutions containing varying concentrations of tastants. Bryant Declaration ¶ 6. The lick ratio of the wild type mice steadily decreased from 1.0 to 0.1 licks per interval as the concentration of denatonium increased from 0.1 mM to about 4 mM. *Id.* The lick ratio of the TRP8 knockout mice, however, did not fall below 1.0 until the denatonium concentration reached about 10 mM. *Id.* Similarly, the lick ratio of the wild type mice steadily decreased from about 0.7 to about 0.1 licks per interval as the concentration of quinine hydrochloride increased from 0.01 mM to about 10 mM. *Id.* The lick ratio of the TRP8 knockout mice, however, did not fall below 0.6 until the quinine hydrochloride concentration reached 1 mM, and never fell below 0.5. *Id.* Thus, the TRP8 knockout mice showed a decreased aversion to both bitter compounds

compared to the response of the wild-type mice. *Id.* These data demonstrate that TRP8 is involved in bitter taste transduction. *Id.*

The present application also teaches that the level of TRP8 activation may be assessed, *e.g.*, by measuring membrane potential. Paragraph [0059]. Dhallan et al., "Primary Structure and Functional Expression of a Cyclic Nucleotide-activated Channel from Olfactory Neurons," *Nature* 347(6289):184–187 (1990) (inside-out patch tests for measuring current flow across kidney cell); Misaka et al., "Taste Buds Have a Cyclic Nucleotide-activated Channel, CNGgust," *J. Bio. Chem.* 272(36):22623–22629 (1997) (inside-out patch tests for measuring current flow across kidney cell); and Altenhofen et al., "Control of Ligand Specificity in Cyclic Nucleotide-gated Channels from Rod Photoreceptors and Olfactory Epithelium," *Proc. Nat'l Acad. Sci. USA* 88:9868–9872 (1991) (*Xenopus* oocyte patch test to measure current flow in photoreceptors and olfactory sensory neurons) (all provided to the PTO on December 21, 2005) demonstrate that assays for measuring membrane potential across cells were well-known in the art at the time of filing. Thus, from the teachings of the present application, one of skill in the art would have known how to measure the change in membrane potential of cells.

The Bryant Declaration confirms that changes in membrane potential may be used to measure TRP8 activation. The effect of carbachol (a surrogate bitter tastant) on membrane potential in wild type HEK 293 cells and HEK 293 cells transfected with TRP8 was evaluated. Bryant Declaration ¶ 8. Carbachol activates the M1 G-protein-coupled receptor, leading to activation of TRP8, which in turn results in an increase in the fluorescence signal of a membrane potential dye. *Id.* This increased fluorescence signal is indicative of a decrease in the cell membrane potential caused by opening of a cation channel. *Id.* After exposure to 30 μM carbachol, cells transfected with TRP8 exhibited an increase from 0 to about 70,000 fluorescence units. *Id.* This signal increase is indicative of cell depolarization where positive ions enter the cell and decrease the membrane potential. *Id.* In contrast, wild type cells exhibited very little change in fluorescence response and hence membrane potential. *Id.* These data demonstrate that membrane potential may be used to measure activation of TRP8. *Id.*

In view of the demonstration in the Bryant Declaration that TRP8 activation is involved in bitter taste transduction and that membrane potential can be used to measure

TRP8 activation, it is apparent that there is a substantial utility for the method of identifying compounds in claims 37–41.

For these reasons, the rejection under 35 U.S.C. § 101 for lack of utility is improper and should be withdrawn.

The rejection of claims 17, 25–33, and 36–41 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed for substantially the reasons discussed above with regard to the rejection under 35 U.S.C. § 101.

The rejection of claims 17, 25–33, and 36–41 under 35 U.S.C. § 112 (1st para.) for lack of written description is respectfully traversed for substantially the reasons set forth in the preceding rejections.

The rejection of claims 17, 25–33, and 36–41 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

Claims 37–41 clearly recite a method for identifying a compound that induces the perception of a bitter taste by contacting an isolated cell expressing the TRP8 channel protein with a test compound and with a control and measuring the level of TRP8 activation by measuring the membrane potential of the cell. The claims further state that an increased level of TRP8 activation in the presence of the test compound indicates that the test compound induces the perception of bitter taste. The Bryant Declaration demonstrates that one of ordinary skill in the art who understands what a membrane potential measurement is would be fully able to understand and carry out the claimed method. Membrane potential is the electrical potential across the cell membrane resulting from the difference in the concentration of charged ions, *i.e.*, net charge, on each side of a membrane. Bryant Declaration ¶ 7. In mammalian cells, including taste cells, the cytoplasmic side of the plasma membrane is usually at a negative potential relative to the outside, *i.e.*, there is generally a net negative charge on the internal side of the membrane and a net positive charge external the membrane. *Id.* Thus, an increase in intracellular cations, *e.g.*, calcium or others, would reduce the net negative charge inside the cell, thereby decreasing the membrane potential, *i.e.*, causing cell depolarization. *Id.* Cell depolarization is also a process often associated with transmitter release in sensory cells. *Id.* The present application teaches that TRP8 activation is associated with increased levels of intracellular calcium and with transmitter release. *Id.*; Present Application ¶¶ [0011], [0060]. Thus, considering that TRP channels were known to be by and large non-selective cation channels, and the known relationships

between cation entry and membrane potential and between depolarization and transmitter release, scientists would understand that an increase in the level of TRP8 activation would be associated with a decrease in membrane potential. *Id.* Based on this understanding, those skilled in the art would recognize that in measuring the level of TRP8 activation by measuring membrane potential, in accordance with the pending claims, a decrease in membrane potential would correlate to an increase in the TRP8 activation level which is indicative of a compound that induces bitter taste.

Accordingly, the indefiniteness rejection under 35 U.S.C. § 112 (2nd para.) is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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